EXPERIMENT K-6-14

HEPATIC FUNCTION IN RATS AFTER SPACEFLIGHT

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SUMMARY

To determine the possible biochemical consequences of prolonged weightlessness on liver function, tissue samples from rats that had flown aboard Cosmos 1887 were analyzed for hepatic protein, glycogen and lipids as well as the activities of a number of key enzymes involved in metabolism of these compounds and xenobiotics. Among the parameters measured, the major differences were elevations in the hepatic glycogen content and HMG-CoA reductase activities of the rats flown on Cosmos 1887, and a decrease in the amount of microsomal cytochrome P_{450} and the activity of aniline hydroxylase, a cytochrome P_{450}-dependent enzyme. Decreases in these two indices of the microsomal mixed-function oxidase system indicate that spaceflight may compromise the ability of liver to metabolize drugs and toxins. The higher HMG-CoA reductase correlated with elevated levels of serum cholesterol. Other changes included somewhat higher blood glucose, creatinine, SGOT, and much greater alkaline phosphatase and BUN. These results generally support the earlier observation of changes in these parameters (Merrill et al., Am. J. Physiol. 252:R22-R226, 1987). The importance of these alterations in liver function is not known; however, they have the potential to complicate long-term spaceflight.

INTRODUCTION

The experience of weightlessness during spaceflight and the stresses associated with lift-off and reentry cause a number of physiological changes in astronauts and experimental animals. These include changes in fluid distribution, electrolyte balance, bone strength and growth, nitrogen balance, and lean body mass, inter alia (1-10). Many of these changes appear to be due to the lack of exercise that occurs in a weightless environment, but whether others represent the influence of long-term stress or other factors remains at issue.

Among the changes that have been observed during and after spaceflight are elevated adrenal steroid secretion and altered concentrations of various lipids and carbohydrates in blood and other tissues. Changes in hepatic concentrations of glycogen, lipids, and enzymes involved in metabolism of these compounds occurred during or after spaceflight in the Cosmos biosatellites (1-3,5,6,11). Secretion of a number of hormones that affect enzyme systems in liver may be altered by space flight; these include adrenal steroids, insulin, and growth hormone (3,8).

Since liver is an important site of nutrient and xenobiotic metabolism, further study of the effects of spaceflight on this organ appeared warranted. The inclusion of experimental animals aboard Spacelab 3 allowed us to conduct analyses of some of the key hepatic enzymes of cholesterol, glycerolipid, and sphingolipid biosynthesis (10) as well as quantiation of glycogen, protein, and lipids. These analyses revealed significantly lower activities for some but not all of the enzymes tested, suggesting that spaceflight can cause specific perturbations in liver function.

Based on these previous findings, we propose that several aspects of hepatic function are altered by spaceflight. In particular, these include key enzymes of cholesterol and sphingolipid biosynthesis and drug metabolism (e.g., cytochrome P_{450}). Described in this report are additional data from analyses of liver and serum samples from rats flown on Cosmos 1887 that support this hypothesis.

MATERIALS AND METHODS

Each group contained five male rats of Czechoslovakia-Wistar origin. They weighed between 300 and 400 g and were fed 55 g/day of a paste diet, and given water ad libitum. The animals were flown for 14 days and maintained on a regular cycle of 16 h of light/8 h of dark. The animals were killed between 53 and 56 hours after landing and the livers were immediately frozen and stored at

-80°. Additional information about the history of the animals and parameters such as the organ weights will be provided by the other participants of this study (e.g., Dr. Richard E. Grindeland, NASA).

Tissue preparation. The liver samples were thawed, homogenized, and centrifuged following fairly standard protocols to yield a microsomal fraction and a high-speed (cytosolic) fraction as described previously (10). We have found this procedure to recover microsomes in approximately 78% yield with little contamination with markers of other subfractions (12). Aliquots of the original homogenate, microsomes, and cytosol were stored at -80° until use. Individual aliquots were used for each assay to minimize losses of activity during freeze/thaw.

Serum analyses. The serum analyses were conducted using a COBAS Bio-centrifugal Analyzer calibrated with certified clininal standards.

Protein analyses. Total protein was assayed using a modification of the method of Lowry et al. (13) with bovine serum albumin as the standard.

Glycogen analyses. Liver glycogen was quantitated using the method of Johnson and Fusaro (14) and rabbit liver glycogen (Sigma Type III) as the standard.

Lipid analyses. The lipids were extracted as described before (10) using essentially the method of Bligh and Dyer (15) and analyzed for triglycerides and cholesterol using the COBAS Analyzer. Phospholipids were quantitated by assaying the amount of organic-solvent soluble phosphate, and the total sphingolipids were estimated by analysis of the sphingosine content after acid hydrolysis (16). Free sphingosine was quantitated by high-performance liquid chromatography (17).

Enzyme assays. Most of the enzyme assays were conducted as described previously (10). Fatty acyl-CoA synthetase was assayed with [^{3}H]palmitic acid as the substrate (18), and HMG-CoA reductase was assayed as described by Shapiro et al. (19), except that the [^{14}C]-HMG-CoA concentration was 25 μM. Serine palmitoyltransferase was assayed using [^{3}H]serine (12,21) and glycerol 3-phosphate acyltransferase using [^{3}H]glycerol 3-phosphate (21). Cytochrome P_{450} was measured spectrophotometrically (22), and aniline hydroxylase was determined as described by Gram et al. (23,24).

Tyrosine aminotransferase (25) and glutathione S-transferase (26) were assayed as described; cystathionase was measured by its ability to produce hydrogen sulfide from cysteine, using assay method III of Stipanuk and Beck (27). Alkaline phosphatase was analyzed as part of the COBAS centrifugal analyzer.

DNA measurement. DNA was quantitated by the method of Fiszer-Szafarz et al. (28) using calf thymus DNA as the standard.

Statistical methods Except where otherwise noted, the data are given as the means ± the standard deviation for n=5 in each group.

RESULTS

General effects of spaceflight on liver. The rats flown on Cosmos 1887 had slighly lower body weights than either the synchronous or vivarium controls; however, the liver weights were similar (Table 1). The groups were also similar in amounts of total liver protein, cytosolic protein, triglycerides, cholesterol and sphingolipids; however, the flight group was somewhat lower in microsomal protein (but only on a per g of liver basis) and total phospholipids. Liver DNA was

lowest for the flight rats (ca. 28% lower than the synchronous controls). The major differences were seen in liver glycogen, which was much lower for the vivarium rats and highest for the flight animals (2-fold higher than the synchronous controls). There appeared to be an inverse relationship between the amounts of DNA and glycogen, which indicates that a partial explanation for the lower cell number per g of tissue is loading of the liver with glycogen.

Liver enzymes of rats after spaceflight. All of the cytosolic enzymes examined exhibited similar activities among the three groups. Even tyrosine aminotransferase, which is highly sensitive to changes in the hormonal status the animal, was not altered significantly (Table 2). Liver alkaline phosphatase, which is primarily a plasma membrane enzyme, appeared slightly higher for the synchronous controls (58.0 $\pm$ 13.7 units/g of liver) than for the flight group (48.8 $\pm$ 3.8 units/g of liver), but the differences were not statistically significant.

Much larger differences were seen in microsomal enzymes (Table 3), without a single trend (i.e., some activities increased while others decreased); hence, the rats that had undergone spaceflight underwent selective changes in microsomal enzymes. HMG-CoA reductase was over 2- fold higher for the flight rats versus both vivarium and synchronous controls (Table 3), and this correlated with the higher serum cholesterol (Fig. 1). Serine palmitoyltransferase and fatty acyl-CoA synthetase were also elevated (by 41% and 58%, respectively), but only on a per g of liver basis.

Cytochrome P_{450} was slightly lower in the flight group (14%), and this persisted when the data were compared on per g of liver (38%) and per 100 g of body weight (21%) bases. Aniline hydroxylase, a member of the microsomal mixed-function oxidase system that utilizes cytochrome P_{450}, was also lower in the flight group (Table 3). Altogether, the similar depressions in cytochrome P_{450} and aniline hydroxylase (Fig. 2) indicate that the xenobiotic metabolizing system is somewhat depressed in the animals that underwent spaceflight.

Effects of spaceflight on serum components. As a broader indicator of the overall biochemical status of these animals, a standard profile of serum components was obtained (Table 3). Total protein, albumin, glucose, bilirubin, Ca^{2+}, K^{+}, and phosphate were virtually identical for the flight group and the synchronous controls.

Markers of muscle and tissue protein trauma (BUN, Creatine, AST, alkaline phosphatase, and lactate dehydrogenase) were consistently elevated in the flight groups (BUN was 144% higher than the synchronous controls). Furthermore, the flight animals were hyperlipidemic, with significant elevations in serum cholesterol (67%) and to a lesser extent triglycerides (16%).

DISCUSSION

Because there was a two day period between the landing of Cosmos 1887 and the removal of the livers for these biochemical analyses, the results of this study are more likely to reflect the combination of spaceflight and the responses of the rats during a post-flight recovery period than to changes due to spaceflight alone. Activities that change with a short half-time, therefore, may easily readjust during or after landing, whereas parameters that require several days to change will remain near the values attained during spaceflight. Nonetheless, many of the findings of this study agreed closely with previous biochemical analyses that were conducted with a shorter lag time.

The most significant results obtained from this analysis of liver function after spaceflight include the findings that glycogen content was elevated in the flight group, that these animals were hyperlipidemic (and had elevations in the initial enzymes of cholesterol and sphingolipid biosynthesis), and that cytochrome P_{450} values were lower than for the synchronous control group.

The major difference from the previous studies (1,10) was in the increase in HMG-CoA reductase activity, which was lower in rats from Spacelab 3. It is clear from these analyses of flight rats that there are specific and unexplained changes in the activities of the initial enzymes of cholesterol and sphingolipid biosynthesis. This finding may be important, since these lipids are primarily involved in cell surface phenomena, such as the functioning of enzymes and receptors, cell-to-cell communication, cell-to-surface antigenicity, and some aspects of nerve impulse transmission. Cholesterol and sphingomyelin are both found in lipoproteins, and these changes may relate as much to the levels of circulating lipids as to those in liver.

Serum cholesterol has been reported to decrease during both Apollo and Skylab missions (4,8). However, plasma cholesterol was higher for the rats on Spacelab 3 (29) and this Cosmos flight, which might indicate that lipoprotein cholesterol was removed from circulation more slowly for these animals. Additional experiments are needed to explain these discrepancies.

The large difference in hepatic glycogen content between flight and control groups confirms the earlier observation with Spacelab 3. Smaller increases in glycogen content have been observed after other missions, as well as significantly decreased activity of glycogen phosphorylase (1,2); and increased glycogen was noted also in heart and skeletal muscle. Since the animals had eaten little during the previous hours, the differences observed may relate to reduced glycogen breakdown in the flight group (however, the synchronous group were fed according to the same schedule). Since hepatic glycogenolysis and gluconeogenesis are critical in maintaining normal blood sugar levels, it is important to determine whether these processes were altered during weightlessness; blood glucose was the same (or slightly elevated) in the flight group at the time of sampling, as has been seen previously (10).

The indication that cytochrome P_{450} was lower in liver from the flight group confirmed the earlier finding with Spacelab 3. This enzyme protein is involved in the metabolism of steroid hormones and a variety of xenobiotics, including antibiotics and other drugs; hence, decreases might reduce the activity of such systems. This was demonstrated in the lower activity of aniline hydroxylase in the flight group. Although these differences were small, the fact that they were seen in two indices of the microsomal mixed function oxidase system lends credence to their validity. The implications of this effect of spaceflight on the body's ability to metabolize drugs have not been explored; however, it could limit the ability of an animal to detoxify various drugs and other compounds, and diminish the potency of drugs that act after bioactivation by the cytochrome P_{450} system.

We conclude that spaceflight significantly alters liver function in a number of ways. Changes in glycogen and lipid metabolism are probably consequences of weightlessness, and drug metabolism may also be altered. Because the liver functions to regulate supply, distribution, and deposition of numerous compounds that are either required by other organs or that can be toxic to them, the bearings of these findings on long-term adaptation to weightlessness should be evaluated in future work. In the future it will be essential to obtain samples taken in flight or shortly after landing to permit valid measurements of these parameters.

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TABLE 1.

Liver Protein, Glycogen, and Lipid Analyses

	Vivarium	Synchronous	Flight
		(Mean ± SD)	
Body weight (g)	342 ± 17.2	349.0 ± 13.0	303.2 ± 5.4
Liver weight (g)	8.27 ± 0.67	8.86 ± 0.42	9.96 ± 3.16
Liver DNA (mg/g liver)	5.11 ± 0.36	3.84 ± 0.83	2.75 ± 0.73
(mg/liver)	42.3 ± 3.4	34.0 ± 7.4	27.4 ± 8.7
(mg/100 g B.W.)	12.4 ± 1.0	9.7 ± 2.1	9.0 ± 2.9
Liver protein			
(mg/g liver)	213 ± 9	215 ± 15	228 ± 19
(g/liver)	1.76 ± 0.14	1.90 ± 0.1	2.27 ± 0.72
(mg/100 g B.W.)	0.51 ± 0.04	0.54 ± 0.03	0.75 ± 0.23
Microsomal protein			
(mg/g liver)	2.8 ± 0.2	3.3 ± 0.3	2.4 ± 0.7
(mg/100 g B.W.)	6.8 ± 0.5	8.4 ± 0.7	7.8 ± 2.2
Cytosolic protein			
(mg/g liver)	112 ± 11	110 ± 6	116 ± 15
Glycogen (mg/g liver)	5.0 ± 1.0	11.5 ± 2.9	20.7 ± 4.6
Total phospholipids			
(μmol/g liver)	32.8 ± 2.3	35.8 ± 1.9	28.6 ± 2.0
Triglycerides			
(mg/g liver)	143 ± 11	151 ± 11	155 ± 19
Cholesterol (mg/g)	7.03 ± 0.63	5.75 ± 1.46	4.69 ± 0.90
Total sphingolipids			
(μmol/g liver)	0.60 ± 0.04	0.58 ± 0.02	0.62 ± 0.06
Free sphingosine			
(nmol/g liver)	4.31 ± 0.80	2.99 ± 0.43	2.93 ± 0.21

TABLE 2.

Activities of selected cytosolic liver enzymes

	Vivarium	Synchronous	Flight
		(Mean ± SD)	
Cytosolic enzymes			
Tyrosine aminotransferase			
(µmol/min/mg protein)	8.29 ± 1.63	6.49 ± 2.18	6.69 ± 2.01
(mmol/min/g liver)	0.93 ± 0.18	0.71 ± 0.24	0.78 ± 0.23
Glutathione S-transferase			
(nmol/min/mg protein)	173 ± 10	191 ± 24	153 ± 24
µmol/min/g liver)	19.4 ± 1.1	21.0 ± 2.6	18.9 ± 2.8
Cystathionase			
(nmol/min/mg protein)	3.20 ± 0.46	3.56 ± 0.69	3.21 ± 0.64
(µmol/min/g liver)	0.36 ± 0.05	0.39 ± 0.08	0.37 ± 0.07
Cystathionine ß-synthase			
(nmol/min/mg protein)	3.27 ± 0.16	2.99 ± 0.82	3.29 ± 0.40
(µmol/min/g liver)	0.37 ± 0.02	0.33 ± 0.09	0.38 ± 0.05

TABLE 3.

Activities of selected microsomal enzymes of rat liver

	Vivarium	Synchronous	Flight
		(Mean ± SD)	
Cytochrome P-450			
(nmol/mg)	0.58 ± 0.15	0.77 ± 0.12	0.66 ± 0.11
(nmol/g liver)	1.62 ± 0.4	2.54 ± 0.4	1.58 ± 0.26
(nmol/100 g B.W.)	3.91 ± 1.01	6.48 ± 1.01	5.15 ± 0.86
Aniline hydroxylase			
(units/mg)	0.048 ± 0.008	0.050 ± 0 008	0.041 ± 0.008
(units/g liver)	0.134 ± 0.022	0.165 ± 0.026	0.098 ± 0.019
(units/100 g B.W.)	0.039 ± 0.006	0.047 ± 0.007	0.032 ± 0.006
Fatty acyl-CoA synthetase			
(nmol/min/mg protein)	34.4 ± 6.6	31.6 ± 3.5	49.9 ± 2.9
(nmol/min/g liver)	96.3 ± 18.5	104 ± 12	119 ± 7
Glycerol 3-phosphate acyltransferase			
(nmol/min/mg protein)	1.23 ± 0.18	1.32 ± 0.04	1.65 ± 0.39
(nmol/min/g liver)	3.44 ± 0.50	4.36 ± 0.13	3.96 ± 0.94
HMG-CoA reductase(μ/mg)	3.7 ± 1.1	4.7 ± 2.6	11.3 ± 4.5
(μ/g liver)	10.4 ± 3.1	15.5 ± 8.6	27.1 ± 10.8
(μ/100 g B.W.)	25.1 ± 7.5	39.5 ± 5.1	88 ± 35
Serine palmitoyltransferase			
(μ/mg)	26.9 ± 2.2	14.5 ± 2.6	20.5 ± 2.0
(μ/g liver)	75.3 ± 6.2	47.9 ± 8.6	49.2 ± 4.8

TABLE 4.
Serum Analyses

	Basal	Vivarium	Synchronous	Flight
		(Mean ± SD, n=5)		
Albumin (g/dL)	5.24 ± 0.17	5.12 ± 0.18	4.96 ± 0.22	4.92 ± 0.27
Total Protein (g/dL)	6.48 ± 0.11	6.60 ± 0.24	6.40 ± 0.24	6.40 ± 0.40
Glucose (mg/dL)	160 ± 6.6	112 ± 18	124 ± 3.8	154 ± 17.2
Total Bili (mg/dL)	0.4 ± 0	0.32 ± 0.11	0.4 ± 0	0.4 ± 0
BUN (mg/dL)	16.8 ± 2.3	17.6 ± 1.7	13.6 ± 1.7	33.2 ± 7.8
Creat mg/dL)	0.52 ± 0.11	0.46 ± 0.23	0.60 ± 0.14	0.84 ± 0.09
AST (SGOT) U/L)	179 ± 66	163 ± 47	193 ± 19	284 ± 70
Alk P'ase U/L)	323 ± 104	105 ± 17	153 ± 16	235 ± 41
LDH U/L)	866 ± 313	694 ± 276	762 ± 96	877 ± 77
Calcium (mg/dL)	10.9 ± 0.1	10.7 ± 0.2	10.1 ± 0.3	9.9 ± 0.4
Phosphate (mg/dL)	7.48 ± 0.41	7.0 ± 0.42	5.96 ± 0.36	6.60 ± 0.40
K (meQ/L)	6.08 ± 0.86	6.16 ± 0.17	5.36 ± 0.09	5.64 ± 0.26
Cholesterol (mg/dL)	62.4 ± 3.6	70.8 ± 12.0	86.0 ± 7.3	128 ± 21
Trig (mg/dL)	182 ± 50	84.8 ± 8.9	122 ± 15	142 ± 34

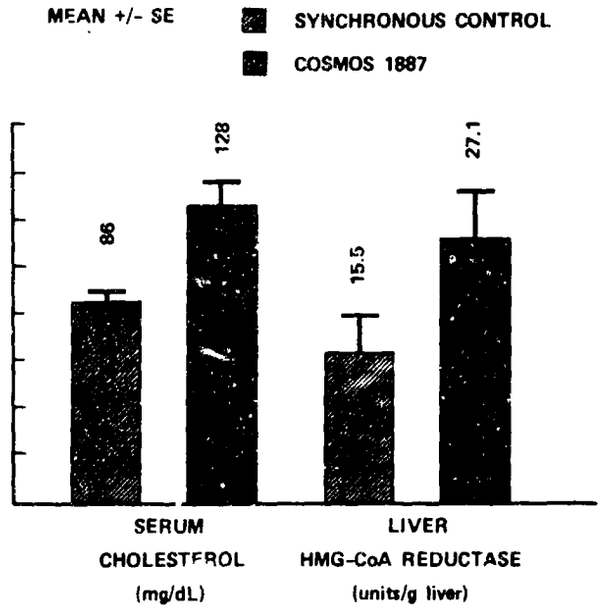

Figure 1. Comparison of serum cholesterol and liver HMG-CoA reductase activities of rats flown on Cosmos 1887 and synchronous controls. The actual amounts or units of activity are shown above the bars.

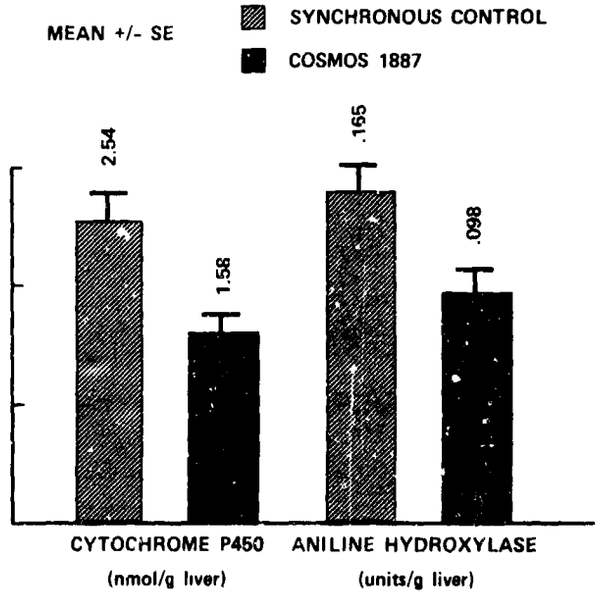

Figure 2. Comparison of microsomal cytochrome P_{450} and aniline hydroxylase activities of rats flown on Cosmos 1887 and synchronous controls. The actual amounts or units of activity are shown above the bars.